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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/627,124	07/25/2003	Maria Tang	10302.200-US	4207

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EXAMINER	
GRASER, JENNIFER E	

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 08/01/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/627,124	TANG ET AL.	
	Examiner	Art Unit	
	Jennifer E. Graser	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *Prel.Amendt. 7/25/03*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,9,12,15,20-23,28,31,34,39-42,47 and 50* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,9,12,15,20-23,28,31,34,39-42,47 and 50* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *25 July 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7/25/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicants have stated in the Preliminary Amendment filed on 7/25/03 that "[c]laims 5-8, 10, 11, 13-14, 16-19, 24-27, 29-30, 32-33, 35-38, 43-46, 48-49, and 51-57 are canceled without prejudice or disclaimer. Claims 50-69 are pending. However, this statement appears to be incorrect.

The pending claims listed in the Preliminary Amendment filed 7/25/03 are claims **1-4, 9, 12, 15, 20-23, 28, 31, 34, 39-42, 47 and 50**. Claims 5-8, 10, 11, 13-14, 16-19, 24-27, 29-30, 32, 33, 35-38, 43-46, and 48-49 are listed as being cancelled. There are no claims greater than claim 50 listed. In the originally filed listing of claims, the claims went up only to claim 57. Claims 51-57 all depend from cancelled claims and are not presented in the updated claiming listing of 7/25/03 so it is being assumed they are cancelled. Claims 58-69 were never before presented. Clarification and correction is requested.

Claims 1-4, 9, 12, 15, 20-23, 28, 31, 34, 39-42, 47 and 50 from the Preliminary Amendment filed 7/25/05 are currently under examination.

Claim Rejections - 35 USC § 112-2nd paragraph

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 1-4, 9, 12, 15, 20-23, 28, 31, 34, 39-42, 47 and 50 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is vague and indefinite because of the term "heterologous biological substance" in lines 1, 3, 4 and 8. "A method of producing a heterologous biological substance" is recited in the preamble and the method set forth appears to be a recombinant protein production method. The term "heterologous biological substance" is vague and indefinite. It is unclear what substance other than a protein could be made by the claimed method. "Heterologous biological substance" is extremely vague and indefinite and could read on ***any*** biological substance not present in *Bacillus*, e.g., oil, blood, mucus, etc.. Page 1 of the specification teaches that the concept of the claimed invention is that removing the red pigment from the *Bacillus* host cells allows for optimal recovery and purification of the transformed protein. Accordingly, the claim should be amended in order to recite "heterologous protein" in lieu of "heterologous biological substance".

Claim 1 is vague and confusing because of the phrase "comprising a modification of at least one of the genes cypX and yvmC". The mere recitation of a name, i.e., cypX and yvmC, to describe the invention is not sufficient to satisfy the Statute's requirement of adequately describing and setting forth the inventive concept. The claim should provide any structural properties, e.g., cypX comprising the nucleotide sequence set forth in SEQ ID NO:1 and yvmC comprising the nucleotides sequence of SEQ ID NO:8, to adequately define the genes. These sequences are critical limitations. While the specification can be used to provide definitive support, the claims are not read in a vacuum. Rather, the claim must be definite and complete in and of itself. Limitations from the specification will not be read into the claims. The claims as they stand are

incomplete and fail to provide adequate structural properties to allow for one to identify what is being claimed.

The phrase "comprising a modification of at least one of the genes cypX and yvmC" in claim 1 is vague and indefinite because it is unclear that a mutation of just one of the genes would result in cessation of the production of red pigment. Further, it is unclear that both these genes are found in the strains. It is also unclear that any *Bacillus* strain, other than *B.subtilis*, comprises these genes. Clarification and/or correction is required.

In claim 1 "modification" should be changed to "mutation" and specifically recite that the mutation results in loss of red pigment production. The claim does not directly correlate the mutation to the loss of pigment. Correction is required.

Claim 1 is also vague and indefinite because it reads as if the desired substance to be produced is actually linked to the mutated cypx or yvmc gene, when the specification teaches it is a cell comprising a mutated red pigment gene into which a recombinant vector is transformed. The claim must be amended to appropriately convey this concept. Currently, the claim reads on using a cell with unmodified cypx or yvmc genes transformed with a vector comprising mutant cypx/yvmc genes.

Claims 4, 9, 23, 29, 42 and 47 are vague and indefinite because it is unclear if the biopolymer and the metabolite are proteins. These terms appear to encompass much more than a protein. The method/host cell recited in claim 1/20 is a recombinant protein production method. Accordingly, claims 4, 9, 23, and 29 must recite that the metabolite/biopolymers are proteins.

Claim 20 is vague and indefinite because of the term "heterologous biological substance". The term "heterologous biological substance" is vague and indefinite. It is unclear what substance other than a protein could be made from the claimed transformed host. "Heterologous biological substance" is extremely vague and indefinite and could read on ***any*** biological substance not present in *Bacillus*, e.g., oil, blood, mucus, etc..

Claim 20 is vague and confusing because of the phrase "comprising a modification of at least one of the genes cypX and yvmC". The mere recitation of a name, i.e., cypX and yvmC, to describe the invention is not sufficient to satisfy the Statute's requirement of adequately describing and setting forth the inventive concept. The claim should provide any structural properties, e.g., cypX comprising the nucleotide sequence set forth in SEQ ID NO:1 and yvmC comprising the nucleotides sequence of SEQ ID NO:8, to adequately define the genes. These sequences are critical limitations. While the specification can be used to provide definitive support, the claims are not read in a vacuum. Rather, the claim must be definite and complete in and of itself. Limitations from the specification will not be read into the claims. The claims as they stand are incomplete and fail to provide adequate structural properties to allow for one to identify what is being claimed.

In claim 20 "modification" should be changed to "mutation" and specifically recite that the mutation results in loss of red pigment production. The claim does not directly correlate the mutation to the loss of pigment. Correction is required.

Claim 20 is also vague and indefinite because it reads as if the claimed cell comprises a nucleic acid for desired substance to be produced in actually linked to the mutated cypx or yvmc gene, when the specification teaches that a cell in which a cypx or yvmc is mutated to abolish red pigment is transformed with a recombinant vector comprising a gene to be expressed. The claim should be amended to appropriately convey this concept. Currently, the claim reads on a cell with unmodified cypx or yvmc genes transformed with a vector comprising mutant cypx/yvmc genes.

Claim 39 is vague and indefinite because of the term "heterologous biological substance". The term "heterologous biological substance" is vague and indefinite. It is unclear what substance other than a protein could be made from the claimed transformed host. "Heterologous biological substance" is extremely vague and indefinite and could read on ***any*** biological substance not present in *Bacillus*, e.g., oil, blood, mucus, etc..

Claim 39 is vague and confusing because of the phrase "comprising a modification of at least one of the genes cypX and yvmC". Additionally, the word 'comprising' is repeated twice. The mere recitation of a name, i.e., cypX and yvmC, to describe the invention is not sufficient to satisfy the Statute's requirement of adequately describing and setting forth the inventive concept. The claim should provide any structural properties, e.g., cypX comprising the nucleotide sequence set forth in SEQ ID NO:1 and yvmC comprising the nucleotides sequence of SEQ ID NO:8, to adequately define the genes. These sequences are critical limitations. While the specification can be used to provide definitive support, the claims are not read in a vacuum. Rather, the

claim must be definite and complete in and of itself. Limitations from the specification will not be read into the claims. The claims as they stand are incomplete and fail to provide adequate structural properties to allow for one to identify what is being claimed.

In claim 39 "modification" should be changed to "mutation" and specifically recite that the mutation results in loss of red pigment production. The claim does not directly correlate the mutation to the loss of pigment. Correction is required.

Claim 39 is also vague and indefinite because it reads as if the claimed cell comprises a nucleic acid for desired substance to be produced is actually linked to the mutated cypx or yvmc gene, when the specification teaches that a cell in which a cypx or yvmc is mutated to abolish red pigment is transformed with a recombinant vector comprising a gene to be expressed. The claim should be amended to appropriately convey this concept. Currently, the claim reads on a cell with unmodified cypx or yvmc genes transformed with a vector comprising mutant cypx/yvmc genes.

Claim Rejections - 35 USC § 112-Scope of Enablement

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-4, 9, 12, 15, 20-23, 28, 31, 34, 39-42, 47 and 50 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for "A method of producing a heterologous protein, comprising: transforming a mutant *B.subtilis* cell, wherein said mutant cell comprises a mutation in the cypX gene comprising SEQ ID NO:1 or the yvmC gene comprising SEQ ID NO: 7, in which said

mutation renders the cell deficient in red pigment compared to a wild-type *B.subtilis* cell comprising said cypX gene comprising SEQ ID NO:1 or the yvmC gene comprising SEQ ID NO: 7, with a recombinant vector comprising a nucleic acid directing synthesis of the heterologous protein and recovering the heterologous protein from the cell"; "a mutant *B.subtilis* cell, wherein said mutant cell comprises a mutation in the cypX gene comprising SEQ ID NO:1 or the yvmC gene comprising SEQ ID NO: 7, in which said mutation renders the cell deficient in red pigment compared to a wild-type cell comprising said cypX gene comprising SEQ ID NO:1 or the yvmC gene comprising SEQ ID NO: 7, and a recombinant vector comprising a nucleic acid directing synthesis of a heterologous protein"; and "A method of obtaining a mutant *B.subtilis* cell, comprising: making a mutation to the cypX gene comprising SEQ ID NO:1 or the yvmC gene comprising SEQ ID NO: 7, in which said mutation renders the cell deficient in red pigment compared to a wild-type *B.subtilis* cell comprising said cypX gene comprising SEQ ID NO:1 or the yvmC gene comprising SEQ ID NO: 7", does not reasonably provide enablement for the scope of the instant claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The instant specification has taught that the *cypX* gene set forth in SEQ ID NO:1 and the *yvmC* gene set forth in SEQ ID NO:7 are responsible for the production of red pigment in *Bacillus subtilis* cells. The specification also teaches that the red pigment formation is not desirable and must be removed during the recovery and purification of a recombinant protein from the cell or the pigment may co-purify with the protein. It is

taught that often cells that have the desirable trait of increased protein expression and secretion possess these red pigment genes. The specification only teaches the *cypX* gene set forth in SEQ ID NO:1 and the *yvmC* gene set forth in SEQ ID NO:7 from *Bacillus subtilis*. It is unclear and unpredictable whether the other 14 species of *Bacillus* recited in claims 12, 31 and 50 possess red pigment genes, much less red pigment genes with the sequences set forth in SEQ ID Nos: 1 and 7. The specification is only enabled for methods which use *B.subtilis* genes and mutations of the *cypX* gene set forth in SEQ ID NO:1 and the *yvmC* gene set forth in SEQ ID NO:7 and not the broad scope of the claims. It would take one of skill in the art undue experimentation to discover new red pigment genes in any of the other 14 species of *Bacillus*. Bacterial species often times do not produce the same proteins. The prior art is silent as to whether any other species of Bacillus possess the *cypX* and *yvmC* proteins and, therefore, it would take one of skill in the art undue experimentation in order to isolate the claimed DNA sequences from any species of bacteria other than *B.subtilis*. Genentech Inc. v. Novo Nordisk A/S (CAFC) 42 USPQ2d 1001 clearly states: "Patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. See Brenner v. Manson, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966) (stating, in context of the utility requirement, that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.") Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification,

reasonable detail must be provided in order to enable members of the public to understand and carry out the invention."

Claim Rejections - 35 USC § 112-Written Description

6. Claims 1-4, 9, 12, 15, 20-23, 28, 31, 34, 39-42, 47 and 50 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant specification has only taught that the *cypX* gene set forth in SEQ ID NO:1 and the *yvmC* gene set forth in SEQ ID NO:7 are responsible for the production of red pigment in *Bacillus subtilis* cells. The specification also teaches that the red pigment formation is not desirable and must be removed during the recovery and purification of a recombinant protein from the cell or the pigment may co-purify with the protein. It is taught that often cells that have the desirable trait of increased protein expression and secretion possess these red pigment genes. The specification only teaches the *cypX* gene set forth in SEQ ID NO:1 and the *yvmC* gene set forth in SEQ ID NO:7 from *Bacillus subtilis*. It is unclear and unpredictable whether the other 14 species of *Bacillus* recited in claims 12, 31 and 50 possess red pigment genes, much less red pigment genes with the sequences set forth in SEQ ID Nos: 1 and 7. The specification only provides adequate written description for methods which use *B.subtilis* genes and

mutations of the *cypX* gene set forth in SEQ ID NO:1 and the *yvmC* gene set forth in SEQ ID NO:7 and not the broad scope of the claims.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116).

Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision (see page 115).

With the exception of SEQ ID NO:1 and 7, the skilled artisan cannot envision the detailed structure of the encompassed polynucleotides and mutant cells. Therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. The product itself is required.

Furthermore, In The Reagents of the University of California v. Eli Lilly (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a

nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...'requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention".

No disclosure, beyond the mere mention of other species of bacteria and potential genes encoding red pigment proteins is made. This is insufficient to provide Written Description to support the generic claims.

Status of Claims:

7. The prior art has taught the complete genome sequence of *Bacillus subtilis.* Further, the prior art teaches hypothetical proteins which are cytochromes and match the protein sequence encoded by SEQ ID NO:1. A hypothetical conserved protein designated yvmC is also deduced from the complete genome sequence and matches SEQ ID NO:8 by 98.8% identity. However, it is not taught that this protein is a red pigment protein.

The prior art does not teach or suggest mutating the cypX gene comprising the nucleotide sequence set forth in SEQ ID NO:1 and/or the yvmC gene comprising the nucleotide sequence of SEQ ID NO:8, much less mutating them in order to stop red pigment production. Mutant bacterial cells comprising these mutated genes are not taught or suggested by the prior art. The instant claims are free of the prior art, but must overcome the 112, 2nd and 1st rejections before they are deemed allowable.

8. Correspondence regarding this application should be directed to Group Art Unit 1645. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Remsen. The faxing of such papers must conform with the notice published in the

Official Gazette, 1096 OG 30 (November 15,1989). The Group 1645 Fax number is 571-273-8300 which is able to receive transmissions 24 hours/day, 7 days/week.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer E. Graser whose telephone number is (571) 272-0858. The examiner can normally be reached on Monday-Friday from 7:00 AM-4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached on (571) 272-0864.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-0500.

JGraser 7/25/05

Jennifer Graser
Primary Examiner
Art Unit 1645